SUPPLEMENTAL DATA

Supplemental Figures

Figure S1: HLH-30 is required for survival against various bacterial strains (related to Figure 2)

(A-E) Survival of wild type and *hlh-30* animals infected with *E. faecalis* (A), *S. enterica* (B), *P. aeruginosa* (C), or grown on nonpathogenic *E. coli* OP50 (D) or heat-killed *P. aeruginosa* (E). ***: $p < 0.0001$ (Log-Rank test compared to empty vector). Statistical analysis can be found in **Table S7**. Experiments are representative of at least two independent trials.

(F) Oxidative stress assay. Results are representative of three independent trials.

(G) Expression of HLH-30-dependent genes, measured by qRT-PCR, in wild type and *hlh-30* animals, exposed to either *S. aureus* or nonpathogenic *E. coli* for 8 h. Data represent mean ± S.E.M. of three independent biological replicates. *: $p < 0.05$, **: $p < 0.01$, ***: $p<0.001$ (two-sample *t* test).

(H-J) Survival of wild type and *hlh-30* mutant animals pre-treated with dsRNA targeting *F43C11.7* (H), *math-38* (I) or *cyp-37B1* (J), and subsequently infected with *S. aureus*. (H) and (I) are results from the same experiment represented in two separate graphs for clarity. *: $p < 0.01$; **: $p < 0.001$ (Log-Rank test compared to empty vector). Statistical analysis can be found in **Table S7**. Experiments are representative of at least two independent trials.

Figure S2: HLH-30-dependent host response to infection (related to Figure 3)

HLH-30-dependent gene fold induction, measured by qRT-PCR in wild type and *hlh-30* mutants infected 8 h with *S. aureus*, relative to uninfected controls. Data represent mean ± S.E.M. of three biological replicates. *: $p < 0,05$; **: $p < 0.01$; ***: $p < 0.001$ (two-sample one-sided *t* test).

Figure S3: HLH-30-regulated antimicrobial genes (related to Figure 4)

(A) HLH-30-dependent gene fold induction, measured by qRT-PCR in wild type and *hlh-30* mutants infected 8 h with *S. aureus*, relative to uninfected controls. Data represent mean ± S.E.M. of three biological replicates. *: $p < 0,05$; **: $p < 0.01$; ***: $p < 0.001$ (two-sample one-sided *t* test).

(B) HLH-30-dependent antimicrobial gene expression, measured by qRT-PCR in *hlh-30* mutants and *hlh-30* mutants expressing HLH-30::GFP infected 8 h with *S. aureus*, relative to wild-type infected controls. Data represent mean ± S.E.M. of three biological replicates. *: $p < 0,05$; **: $p < 0.01$; ***: $p < 0.001$ (two-sample *t* test).

Figure S4: HLH-30-regulated autophagy and lysosomal genes (related to Figure 5)

(A) HLH-30-dependent gene fold induction, measured by qRT-PCR in wild type and *hlh-30* mutants infected 8 h with *S. aureus*, relative to uninfected controls. Data represent mean ± S.E.M. of three biological replicates. *: $p < 0,05$; **: $p < 0.01$; ***: $p < 0.001$ (two-sample one-sided *t* test).

(B) Simplified model of autophagy in *C. elegans* indicating proposed points of action of the autophagy genes studied in the present work. Green membranes indicate

recruitment of LGG-1::GFP. Based on (Klionsky et al., 2010; Kuballa et al., 2012; Megalou and Tavernarakis, 2009; Mizushima et al., 2010).

(C-F) Representative epifluorescence micrograph of wild type (B, D) and *hlh-30* (C, E) animals expressing GFP::LGG-1. Animals were fed *E. coli* (B, C) or infected with *S. aureus* for 24 h (D, E). *: arrested oocytes.

(G) Quantification of GFP::LGG-1 expression in anterior intestinal epithelial cells (IECs); data represent mean intensity ± S.E.M., N = 16-21 animals per condition. *: $p < 0,05$; **: $p < 0.01$; ***: $p < 0.001$ (two-sample *t* test).

(H) HLH-30-dependent gene expression, measured by qRT-PCR in *hlh-30* mutant and *hlh-30* mutant expressing HLH-30::GFP infected 8 h with *S. aureus*, relative to wild-type infected controls. Data represent mean ± S.E.M. of three biological replicates. *: $p < 0,05$; **: $p < 0.01$; ***: $p < 0.001$ (two-sample *t* test).

Figure S5: TFEB-regulated immune response to S. aureus infection (related to Figure 7)

(A) Cytokine and chemokine expression, measured by qRT-PCR, in RAW264.7 cells transfected with siRNA for 48 h and subsequently infected for 4 h with *S. aureus vs* vehicle (uninf.).

(B-C) Bioinformatic detection of candidate TFEB target immune genes (from HeLa cells overexpressing GFP-TFEB) induced in human monocyte-derived macrophages infected with *S. aureus,* using Nextbio. (B) Statistically significant overlap of both gene sets; (C) statistically significant positive correlation between genes upregulated in both sets (UP).

(D) Curated GSEA of candidate TFEB target genes induced in human macrophages, defined in (B), showing over-represented functional categories related to host defense.

(E) Expression of murine candidate TFEB target genes, measured by qRT-PCR, in RAW264.7 cells stably expressing TFEB-FLAG that were infected for 4 and 8 h with *S. aureus,* normalized to uninfected controls. Data represent means ± S.E.M. of three biological replicates. *: $p < 0,05$; **: $p < 0.01$; ***: $p< 0.001$ (two-sample *t* test).

(F-G) Immune-related gene expression, measured by qRT-PCR, in RAW264.7 cells transfected 48 h with 50nM of control siRNA (siCtrl) or siRNA targeting TFEB (siTFEB #1 and siTFEB #2), and subsequently vehicle-treated (Uninf.) or infected 4 h with *S. aureus*. Data represent mean ± S.E.M. of 4-5 independent replicates. *: $p < 0.05$, ***: $p<0.001$ (two-sample *t* test).

Supplemental Tables

Table S1: RNA-Seq reads (related to Figure 2)

Table S2: *S. aureus*-induced genes (related to Figure 2)

Table S3: HLH-30-dependent *S. aureus*-induced genes (related to Figure 2)

Table S4: Genes induced by *S. aureus* in *hlh-30* mutants (related to Figure 2)

Table S5: HLH-30-independent *S. aureus*-induced genes (related to Figure 2)

Table S6: HLH-30-dependent *S. aureus*-induced genes containing E-box motif in 2 Kb upstream of transcription start site (related to Figure 2)

Table S7: Survival statistics (related to all figures with lifespan and pathogenesis assays)

Table S8: GSEA of HLH-30-dependent *S. aureus*-induced genes (related to Figure 3)

SUPPLEMENTAL EXPERIMENTAL PROCEDURES

C. elegans strains used in this study

Strain	Relevant genotype	Source	Reference
N2 Bristol	wild type	CGC	
VT1584	*hlh-30(tm1978)IV*	Victor Ambros (UMass)	(Grove et al., 2009)
JIN1670*	jinEx14[*rol-6(su1006)*]	This study	
JIN1621#	*hlh-30(tm1978);* jinEx14[*rol-6(su1006*]	This study	
JIN1679*	jinEx10[*hlh-30p::hlh-30::gfp,rol-6(su1006)*]	This study	
JIN1616#	*hlh-30(tm1978*); jinEx10[*hlh-30p::hlh-30::gfp, rol-6(su1006)*]	This study	
DA2123	adIs2122[*lgg-1p::gfp::lgg-1, rol-6(su1006)*]	CGC	(Melendez et al., 2003)
JIN1652#	*hlh-30(tm1978);* adIs2122[*lgg-1p::GFP::lgg-1, rol-6(su1006)*]	This study	

*JIN1670 and JIN1679 were obtained by gonadal microinjection in wild type young adults using pPRF4-*rol-6* (100 ng/µl) or a mix containing pKA674-*hlh-30p::hlh-30::gfp* plasmid (10 ng/µl) and pPRF4-*rol-6(su1006)* (100 ng/µl) as a selection marker.

#JIN1670, JIN1679 and DA2123 were crossed into the *hlh-30* mutant background to generate JIN1621, JIN1616 and JIN1652, respectively. Primer sequences for *hlh-30(tm1978)IV* deletion genotyping are available upon request.

JIB0344 plasmid construction

JIB0344 (pKA674-*hlh-30p*::*hlh-30::gfp)* expression plasmid was obtained by LR recombination (Gateway system, Life Technologies) using pDONRP4-P1R-*hlh-30p* (Open Biosystems), pDONR201-HLH-30a ORF (Vidal ORFeome library) and pKA674 expression plasmid (a generous gift from Kaveh Ashrafi, UCSF). HLH-30a ORF was sequenced and amino acids 123 and 255 were found to diverge from the corresponding RefSeq file (NP_500462.1). Both were restored to wild type using QuickChange Site-Directed Mutagenesis (Stratagene).

Phylogenetic analysis of HLH-30

For identification of MiT homologs in *C. elegans,* the TFEB RefSeq file (accession NP_001161299.1) was BLASTed using the NCBI BLASTP tool (http://blast.ncbi.nlm.nih.gov). BLAST results were visualized with the Distance Tree tool on the same website, using the Neighbor joining method at a cutoff sequence difference of 0.85. Identified *C. elegans* sequences NP_001122513.1, NP_499472.1, NP_001040680.1, AAC13874.1, NP_495938.4, NP_001255308.1, NP_001255775.1, NP_001255776.1, NP_001021581.1, AAA21347.1, NP_001251327.1, NP_001022773.1, NP_505856.1, NP_509976.1, NP_496204.1, NP_500281.1, NP_001251326.1, AAL50027.1, AF213473_1, NP_498631.2, NP_493363.1, NP_494604.1, NP_509136.1, AAB38323.1, NP_510223.1 were then aligned with human MITF (526 aa; Accession ID: O75030), TFEC (318 aa; Accession ID: NP_001018068), TFE3 (470 aa; Accession ID: CAA65800), and TFEB using the Clustal

Omega multiple protein sequence alignment tool at EMBL-EBI (Goujon et al., 2010). The resulting tree was rendered and edited in FigTree (http://tree.bio.ed.ac.uk/software/figtree).

C. elegans infection by S. aureus for RNA analysis

To prepare infection plates, *S. aureus* NCTC8325 was grown overnight (ON) in tryptic soy broth (TSB, BD) with 10 µg/ml nalidixic acid (NAL, Sigma). 500 µl of the ON culture was uniformly spread onto the entire surface of 10 cm tryptic soy agar plates (TSA, BD) supplemented with 10 µg/ml NAL and incubated 6 h at 37 °C, then stored at 4 °C overnight. To prepare control plates, 500 µl of heat-killed (HK) *E. coli* OP50 culture concentrated 10X was plated on TSA + NAL plates. Synchronized wild type and *hlh-30* young adults were seeded the next day on infection and control plates that were previously warmed to room temperature. After 8 h incubation at 25 °C, *S. aureus* infected and HK *E. coli* uninfected animals were washed twice in water and lysed by resuspension in Tri Reagent (Molecular Research Center). After purification, RNA was reverse transcribed as described in the **Experimental Procedures** and analyzed by qPCR or by sequencing. Two independent replicate sample sets were submitted for pooled sequencing at the Genome Technology Access Center at Washington University in St. Louis.

RNA-sequencing analysis

Single-read 1x49-bp sequencing was performed on the Illumina platform to yield 49 bp-

long barcoded reads, with 7 bases designated to distinguish between the eight samples in the pool (see **Table S1**). After removing barcodes, raw 42-bp reads were aligned to the WS190 assembly of the *C. elegans* genome (both gene transfer format files for protein-coding genes and RNA genes were downloaded from the UCSC Browser) using TopHat (Trapnell et al., 2012). Transcript abundance on a per-gene basis was estimated and normalized as FPKMs (Mortazavi et al., 2008) using Partek® software (version 6.3 Copyright © 2008 Partek Inc., St. Louis, MO, USA). We used DESeq (Anders and Huber, 2010) to determine *S. aureus* - induced genes, retaining those that were significantly induced in infected vs. uninfected wild type animals, at $p \leq 0.05$ after multiple test correction (See **Table S2**). To identify HLH-30-dependent *S. aureus*-induced genes, we filtered genes from the wild type list that no longer were induced at $p \leq 0.05$ between infected and uninfected *hlh-30* animals (see **Table S3 and S4**). HLH-30-independent *S. aureus*-induced genes were defined as genes that were induced at $p \leq 0.05$ in both genetic backgrounds (see **Table S4 and S5**).

Discovery of HLH-30-dependent genes potentially regulated by conserved MAGMA exemplar sites

Using PeakAnalyzer (Salmon-Divon et al., 2010), we mapped previously discovered exemplar sites to their nearest genes. We searched for sites that occurred within the nearest upstream 2 kb of intergenic region of genes or overlapping genic regions. The result is a list of exemplar sites and genes that are within close proximity (see **Table S6**). These genes are thought to be the putative targets of regulatory events occurring

at these *cis* sites. A one-tailed, 2x2 Fisher's exact test was performed to determine if the observed overlap of motif-related genes and expression-related genes occurs more than expected by chance. For each pair of gene lists, a p-value is determined from the hypergeometric distribution.

RNAi by feeding

RNAi was carried out using bacterial feeding RNAi (Timmons et al., 2001). HT115 RNAi clones were obtained from the Ahringer genomic RNAi library, or the Vidal library when absent in the former. Clone identity was confirmed by sequencing, and absence of off-target effects was verified against predictions by the *C. elegans* genomic database resource, WormBase (www.wormbase.org). For *cdc-25.1* RNAi knockdown, L4 animals were incubated on *cdc-25.1* RNAi HT115 bacteria for 24 h at 15 °C before transfer to killing plates. For HLH-30-dependent gene knockdown, young adults were incubated 4 days at 15 °C on *E. coli* HT115 RNAi plates, so that the progeny was exposed to dsRNA from embryo to L4 stage.

Killing assay plate preparation

S. aureus NCTC8325 was grown overnight in TSB + 10 µg/ml NAL. 10 µl of overnight (ON) cultures was uniformly spread on 35 mm TSA (BD) plates with 10 µg/ml NAL, and incubated 4-6 h at 37 °C. *P. aeruginosa* PA14 was grown overnight in Luria Browth (LB, BD). 10 µl of ON cultures was uniformly spread on 35 mm slow-killing plates, which contained modified NGM, 0.35% peptone, incubated 24 h at 37 °C then 24 h at 25 °C,

before adding 80–100 µg/ml 5- fluorodeoxyuridine (FUDR, Sigma), to prevent progeny hatching. *E. faecalis* V583 was grown 5 h at 37 °C in Brain Heart Infusion (BHI, BD) supplemented with 50 µg/ml gentamycin. 10 µl of the culture was uniformly spread on 35 mm BHI plates with 50 µg/ml gentamycin and incubated at 37 °C overnight. *S. enterica* SL1344 was grown overnight in LB with 100 µg/ml ampicillin. 10 µl of ON culture was uniformly spread on 35 mm slow-killing plates and incubated 12 h at 37 °C.

Killing assays

For *S. aureus*, *S. enterica* and *E. faecalis* killing assays, 25 – 40 infertile (Emb) *cdc-25.1* RNAi-treated animals were transferred to each of three replicate plates per strain. For *S. aureus* killing assays involving RNAi of HLH-30-dependent genes, RNAi-treated L4 larvae were first transferred onto new HT115 RNAi plates supplemented with 80 -100 µg/ml FUDR for 24 h at 15 °C before transfer to *S. aureus* plates. For *P. aeruginosa*, 25 – 40 L4 hermaphrodites were transferred to each of three replicate plates per strain. Animals that died of bursting vulva or crawling off the agar were censored. Experiments were performed at least twice.

Longevity assays

For *E. coli* OP50 longevity assay, animals were transferred to NGM + OP50 plates supplemented with 80 – 100 µg/ml FUDR and incubated at 25 °C. For longevity assay on heat-killed (HK) PA14, overnight cultures of bacteria were concentrated 10X and incubated at 95 °C for 30 min. 200 µl of HK PA14 was seeded on 35 mm NGM plates

supplemented with 80 – 100 µg/ml FUDR and 100 µg/ml kanamycin. For longevity assays involving RNAi of autophagy or lysozyme genes, RNAi-treated L4 larvae were transferred onto fresh HT115 RNAi plates supplemented with 80 – 100 µg/ml FUDR and incubated at 25 °C. Experiments were performed at least twice.

Oxidative stress assays

Young adult animals were incubated in 100 mM paraquat in M9 buffer, as described (Lee et al., 2010). Surviving animals were identified by visual inspection under the dissection microscope.

Survival statistics

Kaplan-Meier survival analyses were performed using software Prism 5 (GraphPad, http://www.graphpad.com). Survival data were compared using the Log-Rank significance test.

Quantitative PCR, Representation and Statistics

Primer pair sequences for qPCR amplification were obtained from ORIGENE or designed using Primer-BLAST (http://www.ncbi.nlm.nih.gov/tools/primer-blast/) and are available upon request. For *C. elegans* experiments, expression values were normalized against the control gene *snb-1*, which did not vary under the conditions being tested. For RAW246.7 cells, expression values were normalized against the mouse housekeeping genes *Gus* and *Gapdh*. For RT^2-Profiler qPCR analysis,

expression values were normalized against five internal control mouse housekeeping genes.

Graphs were generated using Prism 5 software. Heat maps and clusters were generated using GENE-E (http://www.broadinstitute.org/cancer/software/GENE-E/). For statistics of relative expression, unpaired two-sample two-sided *t* tests were performed using ΔCt values. For statistics of fold induction in wild type animals and *hlh-30* animals (**Figure S3**), unpaired two-sample one-sided *t* tests was performed using ΔCt values from infected animals compared to uninfected controls. p values less than 0.05 were considered statistically significant. *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

Colony Forming Unit (C.F.U) Assay in C. elegans

Exposure of wild type, *hlh-30* mutants, and RNAi-treated wild type animals to *S. aureus* was carried out as for killing assays. Briefly, wild type and *hlh-30* mutant L4 animals were sterilized by one day of growth on *cdc-25.1*-expressing *E. coli* HT115 at 15 °C, then picked to full lawns of *S. aureus* strain NCTC8325 on TSA NAL plates. Otherwise, wild-type RNAi-treated L4 larvae were first transferred onto new *E. coli* HT115 RNAi plates supplemented with 80-100 µg/ml FUDR for 24 h at 15 °C before being transferred onto *S. aureus* plates. At each timepoint of infection and for each genotype or RNAi treatment, 10 animals were collected in 25 mM levamisole hydrochloride (MP Biomedicals) from each of 3 replicate plates and then surface-sterilized for 45 min at room temperature in 25 mM levamisole hydrochloride supplemented with 100 µg/ml kanamycin. After three washes in 25 mM levamisole without antibiotic and

resuspension in 25 mM levamisole 0.1 % Triton X100, an aliquot of the supernatant was removed from each replicate to test for external bacterial contamination. To the remaining solution was added an equal volume of 1 mm silicon carbide beads (BioSpec Products Inc.). Animals were homogenized by vortexing at full speed for 1 minute. Dilution series of control aliquots and homogenates were spread on TSA NAL. C.F.U. counts from the pre-homogenized samples were subtracted from the total homogenized C.F.U. value before calculating C.F.U. per animal.

Colony Forming Unit (C.F.U) Assay in RAW264.7 cells

S. aureus NCTC8325 strain was grown as described in **Experimental Procedures**. Infected cells were immediately incubated on ice to allow bacterial binding while preventing phagocytosis. After 30 min incubation, cells were rinsed 3 times in PBS and either lysed (to quantify external bound bacteria) or incubated 30 min with DMEM 10% FBS to allow bacterial phagocytosis followed by incubation in DMEM 10% FBS supplemented with 100 μg/ml gentamicin to kill external bacteria for the following lengths of time: 30 min (to quantify internalized bacteria at 1 h) and 210 min (to quantify internalized bacteria at 4 h). Infected cells were lysed in PBS 0.1% Triton X100. Serially diluted aliquots were spread on TSA NAL plates and incubated overnight at 37 °C, and C.F.U. were counted the next day.

Immunoblotting

Infected cells were solubilized in RIPA buffer supplemented with Complete Protease

Inhibitor (Roche) and with 20 mM NaF, 1 mM PMSF, 5 mM DTT, and 20 mM β-glycerophosphate. Proteins were loaded on 4-12 % Bis-Tris gels (NUPAGE, Invitrogen), transferred to PVDF membranes, and analyzed by immunoblot using the ECL method (Millipore). The following antibodies were used: anti-FLAG mouse monoclonal antibody (Clone M2 - Sigma), anti-TFEB polyclonal antibody (Bethyl Laboratories), anti-actin monoclonal antibody (clone C4 - Millipore), anti-LSD1 polyclonal antibody (Cell signaling), anti-GAPDH monoclonal antibody (Abcam), horseradish peroxidase (HRP)-conjugated goat anti-mouse (DAKO), HRP-conjugated goat anti-rabbit antibody (Cell signaling).

Cell Fractionation

RAW264.7 cells were fractionated using NE-PER Nuclear and Cytoplasmic Extraction Reagents (Pierce) following manufacturer's procedures. Protein extracts from each fraction were analyzed by immunoblotting.

λ phosphatase assay

RAW264.7 cells were lysed in RIPA buffer, incubated 10 min with agitation at 4 °C, and centrifuged 10,000g for 10 min. Supernatants were treated with λ phosphatase (New England Biolabs) for 30 min at 30 °C and then analyzed by immunoblotting.

Cell Immunofluorescence

Cells were fixed in PBS 4% paraformaldehyde, and labeled with 1:400 anti-Flag M2 antibody before staining with 1:400 Alexa Fluor® 488 Rabbit anti-mouse antibody (Life technologies). Nuclei were stained with Hoechst 33342 Fluorescent Nucleic Acid Stain (ImmunoChemistry technologies). Coverslips were mounted using Prolong anti-fade kit (Molecular Probes).

C. elegans preparation for imaging

HLH-30::GFP and GFP::LGG-1 expressing animals were paralyzed with 10% NaN_3 and mounted on a slide containing a 2% agarose pad for imaging. For HLH-30::GFP animals infected with *S. aureus*, L4 animals were incubated on *cdc-25.1* RNAi bacteria for 24 h at 15 °C, then kept for 2 h at room temperature, before transfer 30 min prior to imaging onto *S. aureus* killing assay plates or TSA supplemented with 10 µg/ml NAL for uninfected control. For GFP::LGG-1 animals, L4 larvae were incubated on *cdc-25.1* RNAi bacteria for 24 h at 15 °C and then transferred to *S. aureus* killing assay plates or to TSA + NAL plates seeded with heat-killed *E. coli* OP50 for uninfected control. Animals were incubated at 25 °C for 8 h (GFP::LGG-1 puncta detection) or 24 h for (GFP::LGG-1 expression detection) before imaging.

Epifluorescence and Confocal Microscopy

HLH-30::GFP and GFP-LGG-1 animals were imaged using the 10X objective in a Nikon Eclipse E800 microscope with Retiga Exi camera and OpenLab software. Imaging of GFP-LGG-1 puncta and RAW264.7 cells was carried out using a 100X oil objective in a Nikon Ti Eclipse inverted microscope with Ultraview Spinning Disc (CSU-X1) confocal

scanner and Orca-ERCamera with Volocity software (Perkin Elmer).

Quantification of GFP levels was performed using ImageJ (NIH); quantification of number of green-positive red-negative puncta (GFP-LGG-1 foci) was performed using Photoshop CS5 (Adobe). Quantification of *hlh-30p::hlh-30::gfp* animals with nuclear localization of HLH- 30::GFP was assessed using a Zeiss Discovery V8 fluorescent dissecting microscope. For statistics, unpaired two-sample two-sided *t* test was performed. p value less than 0.05 was considered statistically significant. *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$, comparing infected with uninfected conditions.

Gene-set enrichment analysis (GSEA)

GSEA was performed using Database for Annotation, Visualization and Integrated Discovery (DAVID) v6.7 (Da Wei Huang, 2009).

Nextbio analysis

Publicly available gene sets of human macrophages stimulated with *S. aureus* (Koziel et al., 2009) and HeLa cells over-expressing TFEB (Sardiello et al., 2009) were analyzed using NextBio (Kupershmidt et al., 2010).

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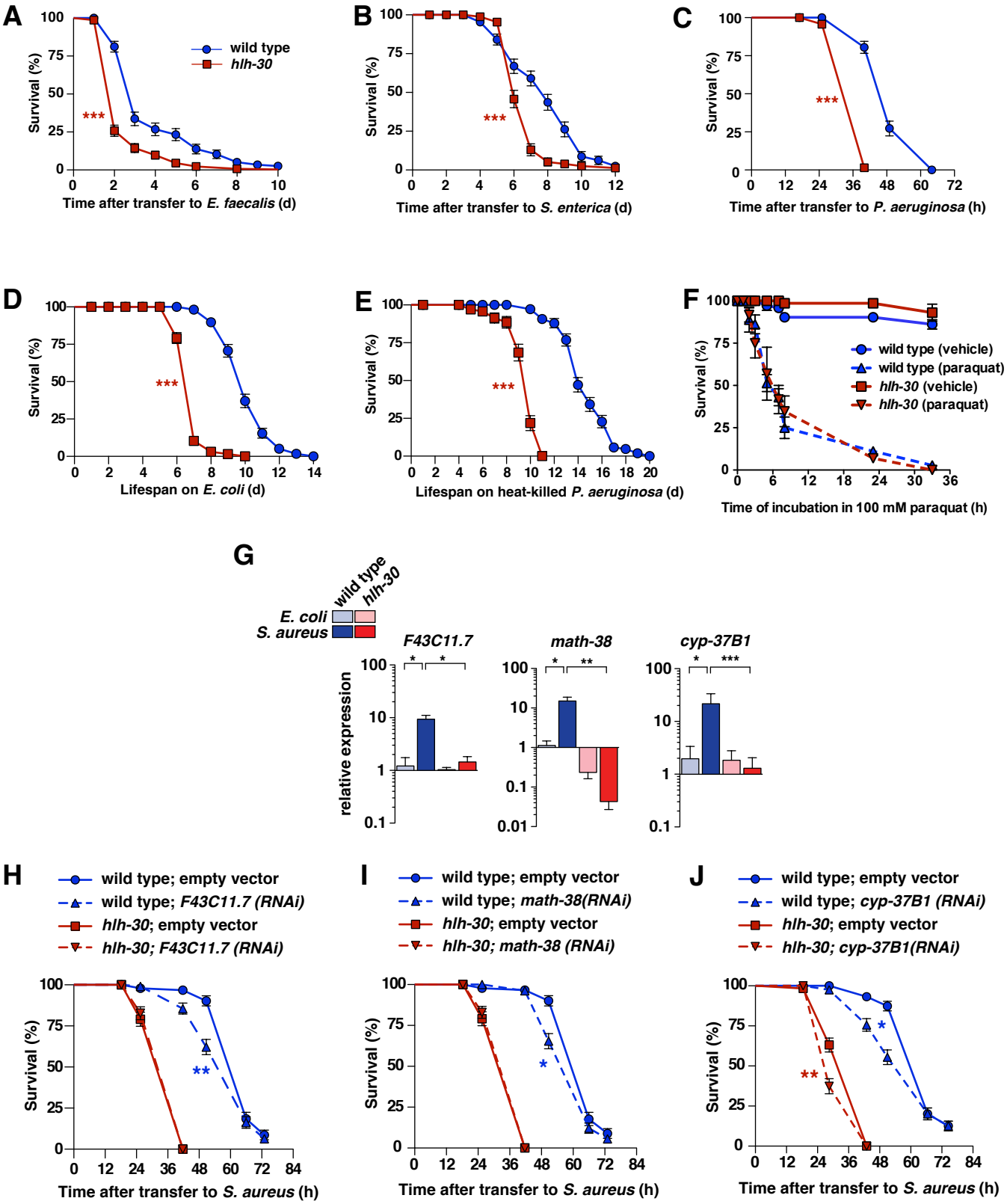
Visvikis Figure S1



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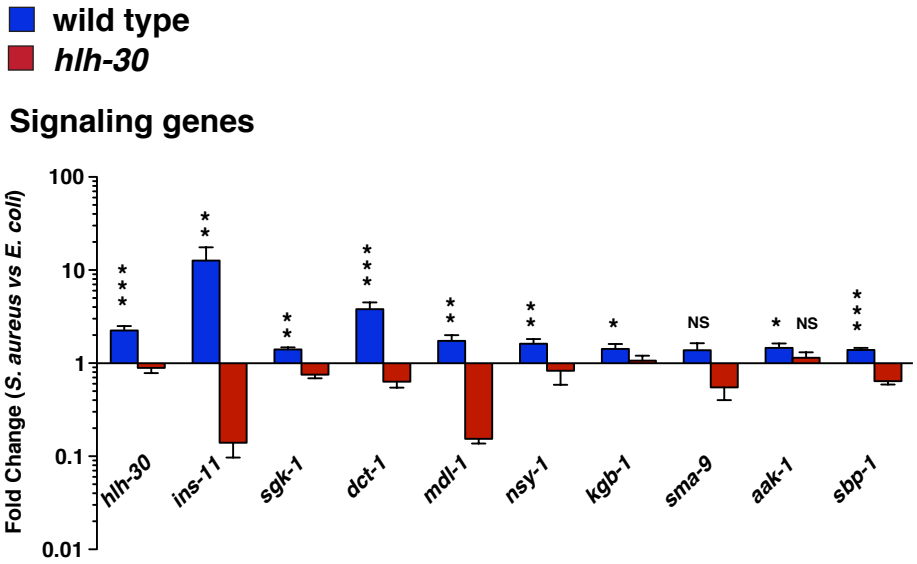

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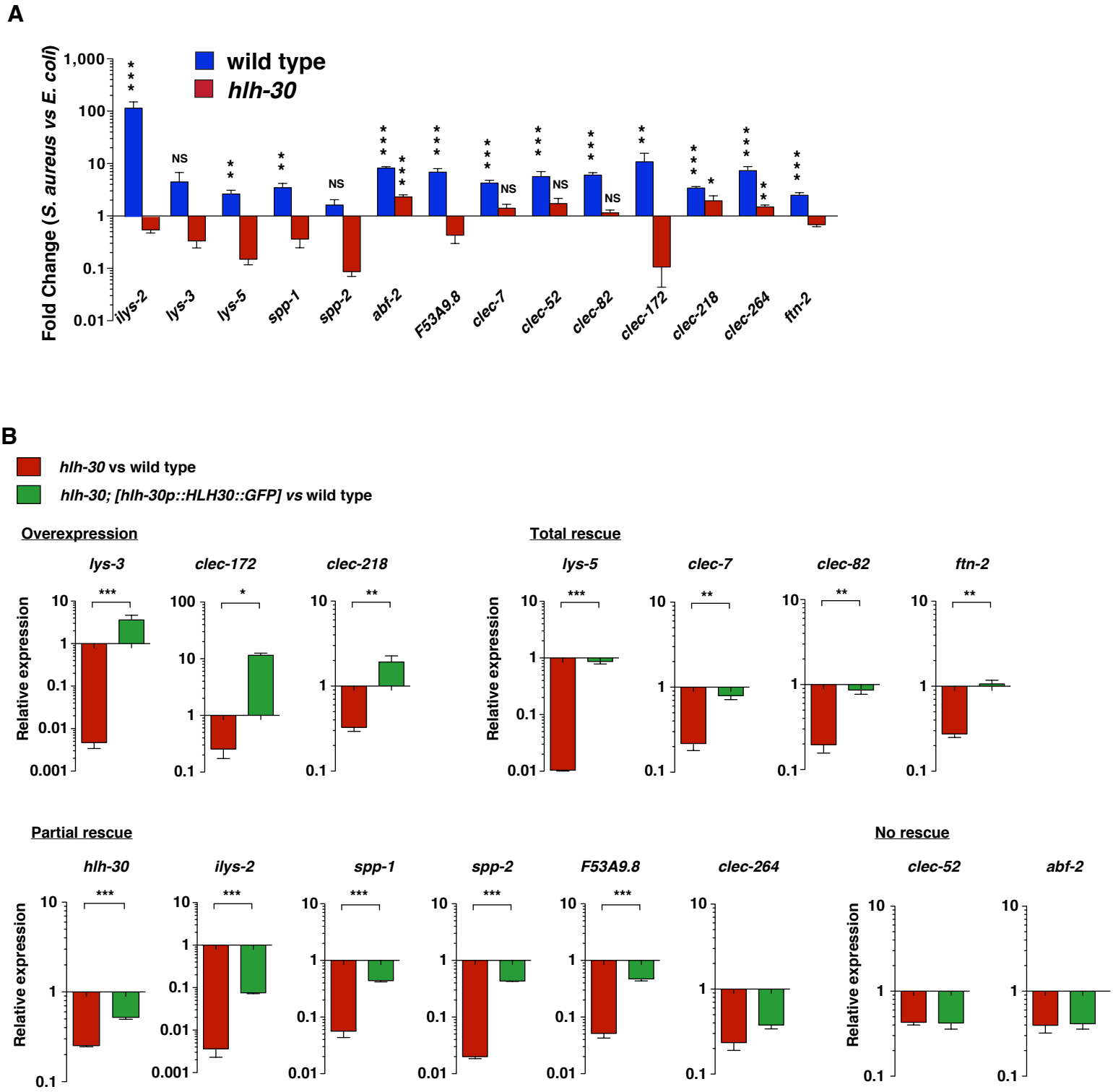

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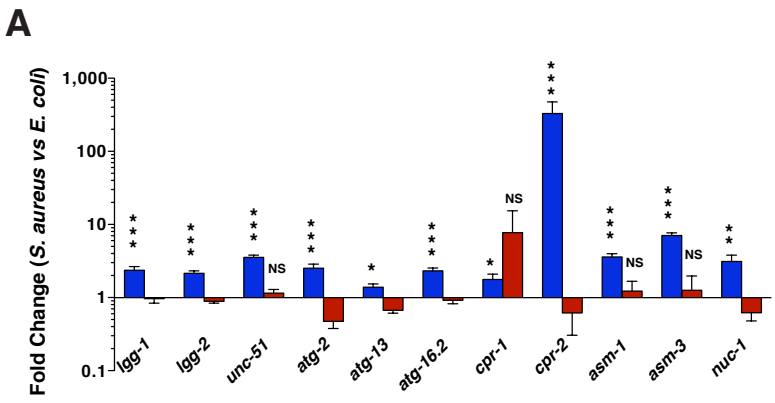

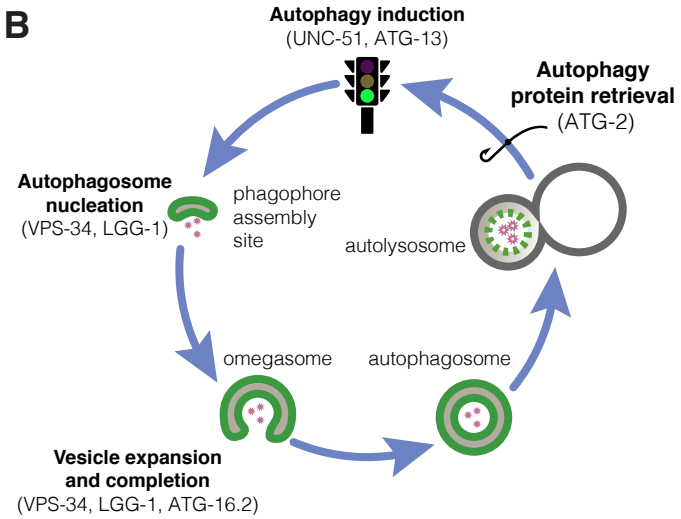

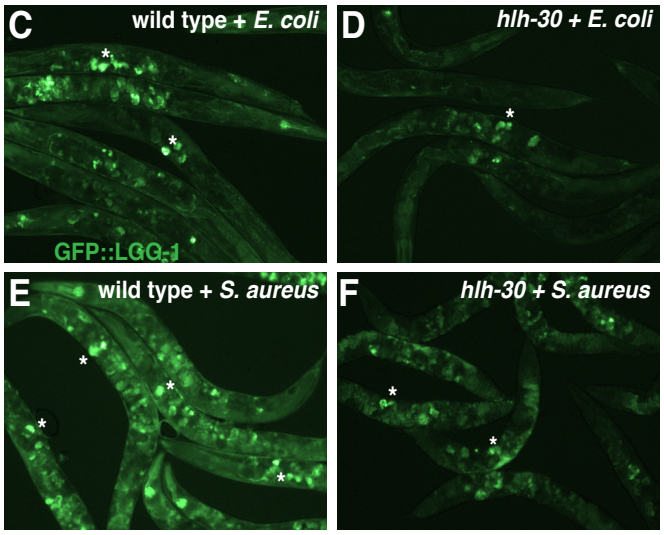

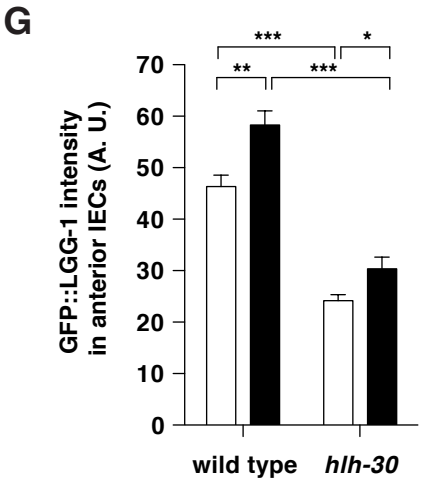

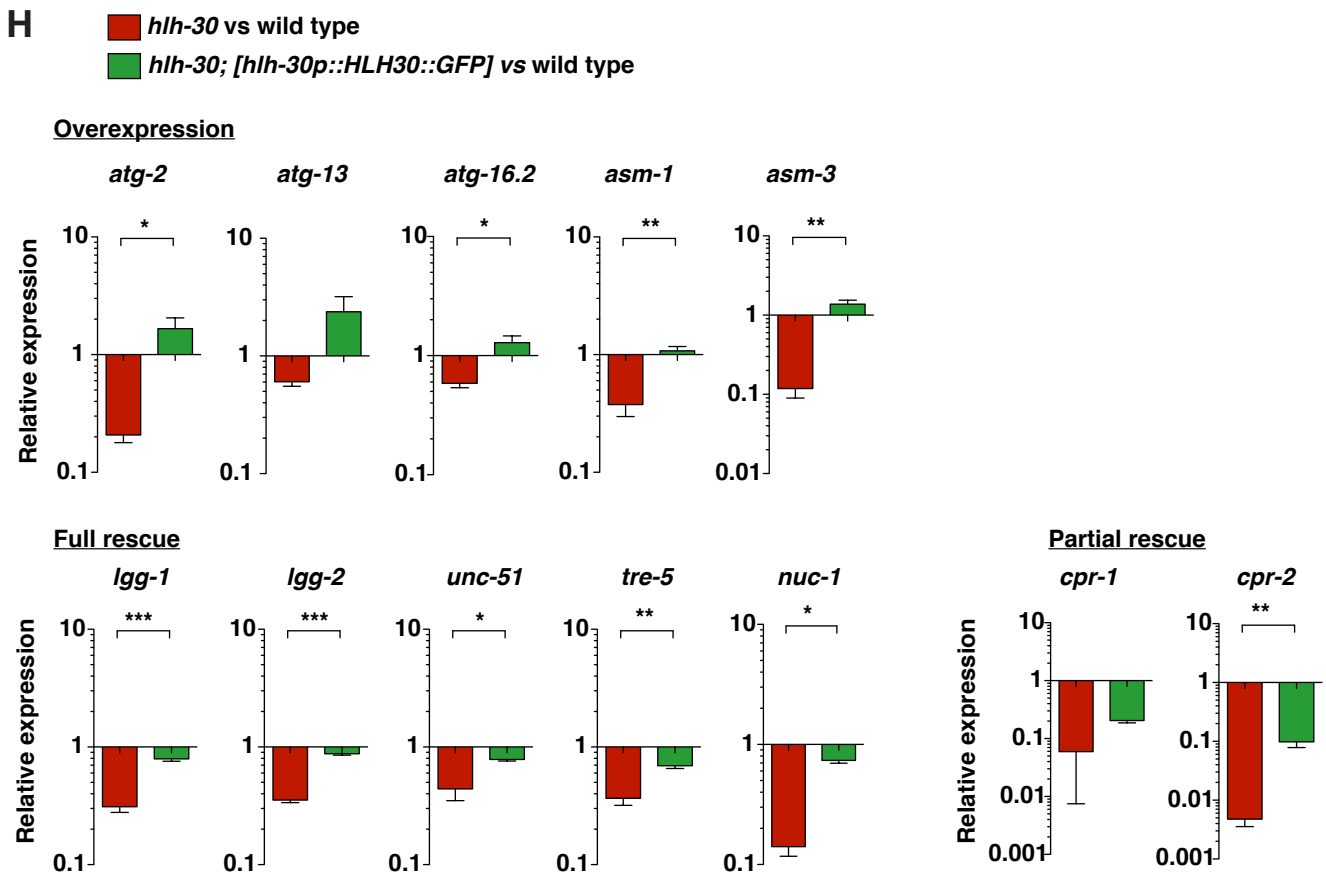

Visvikis Figure S5